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Amiodarone and the Heart

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Abstract

Amiodarone is an old medication that has been used for more than five decades for prevention and treatment of different types of arrhythmias. It is very effective drug however it only used with caution as it carries a risk for serious and sometimes life-threatening adverse events. This review article will give an overview on its discovery, pharmacology, drug interaction, indications and side effects in order to use it efficiently and safely in patients with arrhythmias.

Keywords:

Amiodarone, ventricular arrhythmia, supraventricular arrhythmia, thyroid dysfunction, lung toxicity

Amiodarone discovery

Amiodarone is a chemical substance that derived from khellin, the active ingredient of khella (Ammi visnaga) that has been growing in North Africa. Khellin was first extracted from khella by an Egyptian scientist Mustapha in 1879, then a study done in Cairo in 1946 showed the beneficial effect of khellin in patients with angina through its coronary dilation properties without causing hypotension. In 1961, Labaz group (Sanofi later) succeeded in development of amiodarone from khellin and after that it used in different cardiovascular disease especially angina and arrhythmias throughout Europe (1). In late 1970s, physician started to use amiodarone in ventricular arrhythmia in America despite late approval by FDA in 1985(2).

Pharmacokinetics

Amiodarone is iodine containing benzofuran derivative with similarity to thyroxin in structure. Amiodarone has widely varied bioavailability that ranges between 22-95% and absorption improved if taken within a meal. Onset of its action after IV single dose is between 1-30 minutes and its duration of action is between 1-3hours. The plasma half-life after single oral dose is 3.2-79.7 hours. Due to its highly lipophilic property, it is highly bounded to plasma protein and has a large volume of distribution. Adipose and skeletal tissues accumulate large amounts of the drug during long term treatment. Metabolism and excretion are mainly hepatic in origin and less than 1% excreted unchanged in urine.

Renal disease dose not influence the pharmacokinetics of amiodarone or its metabolites. Main active metabolite is desethylamiodarone (DEA) by the cytochrome P450 enzyme group (CYP3A and CYP2C8). Therapeutic serum concentration ranges between 1.0-3.5mic/ml. It has a reduced clearance rate and long half-life. Elimination half-life is highly variable and averaging about 58 days and up to 100 days. Amiodarone and DEA cross the placenta and both appear in breast milk. Neither amiodarone nor DEA is dialyzable (3,4).

Mechanism of action

Amiodarone is considered as class III antiarrhythmic drug but also it has action similar to all classes of anti-arrhythmics. It blocks sodium, potassium and calcium channels and has anti-sympathetic action as well. It causes prolongation of action potential and repolarization of the myocardium. Also it has a vasodilator effect so decreasing cardiac work and oxygen consumption (5, 6).

Drug interactions

Avoid concomitant use of drugs that cause QT prolongation due to risk of developing Torsade de Pointes. Concomitant use of drugs with depressant effects of sinoatrial node or atrioventricular node can cause significant bradycardia, sinus arrest, and AV block. Close observation of heart rate is essential. Amiodarone is metabolized by Cytochrome P450 enzyme group and so concomitant use of enzyme inducer or inhibitor can lead to decrease or increase effect of amiodarone respectively. Amiodarone and its metabolite DEA are inhibitors of certain CYP450 enzymes and can lead to increase concentration of drugs metabolized by them like procainamide and flecainide. Also, digoxin level increases with amiodarone and precipitate digoxin toxicity. Amiodarone also can increase the level of statin especially simvastatin and this can be associated with rhabdomyolysis and rosuvastatin can be used in such cases (39). It potentiates the effect of warfarin by 100% within 3-4 days of concomitant administration and it is recommended to decrease warfarin dose and monitor INR closely. Cyclosporine concentration also increases with amiodarone and can leads to cyclosporine toxicity and renal impairment. Also, phenytoin levels increase with concomitant use of amiodarone. Significant bradycardia is noticed when antiviral ledipasvir/Sofosbuvir or Sofosbuvir/Simeprevir used in patient receiving amiodarone (7, 8).

Amiodarone is Category D in pregnancy and should not be used in lactation (3, 4).

Cardiovascular Indications of amiodarone

Amiodarone is a class III antiarrhythmic and used in prevention and treatment of different types of ventricular and supraventricular arrhythmias

1-Ventricular arrhythmia:

Ventricular arrhythmia associated with heart failure

It is well known that patients with heart failure have a higher risk of developing different types of ventricular arrhythmias and even sudden cardiac death. Several studies including different patient populations either ischemic or non-ischemic have been conducted to assess the benefits of amiodarone in heart failure in both primary and secondary prevention. Amiodarone decreased the incidence of arrhythmic deaths by 35% - 48% in patients with ischemic cardiomyopathy; however it was not associated with improved overall mortality (9,10). Another study found that amiodarone is even associated with improved all-cause mortality before beta blocker era (11). Also another study showed that amiodarone suppress ventricular arrhythmias and even improved ventricular function in ischemic and non-ischemic patients with heart failure and reduced ejection fraction (HFrEF) who have > 10 premature ventricular contractions (PVCs) /h (12). A study included patients who had an ICD and found that amiodarone when combined with beta blockers has reduced the number of appropriate and inappropriate shocks from ICD by inhibiting both ventricular and supraventricular arrhythmias as well as slowing the heart rate if occurred (13). A meta-analysis included 8522 patients from 15 trials showed that amiodarone decrease the incidence of sudden cardiac death and cardiovascular mortality significantly when compared to placebo or other antiarrhythmic and also all-cause mortality decreased but not reach statistical difference. However, in this meta-analysis 10% of patients discontinue amiodarone therapy compared to placebo due to its side effects (14).

Ventricular arrhythmia associated with acute myocardial infarction

Myocardial infarction is associated with increased frequency of various types of arrhythmia and even sudden cardiac death. Revascularization is the treatment of choice and beta blockers are the best option in absence of decompensated heart failure. Amiodarone is first choice if ventricular arrhythmia occurs in the setting of myocardial infarction in decompensated heart failure. Stable and unstable sustained ventricular tachycardia respond well to amiodarone and better to continue amiodarone infusion for 48h to avoid recurrence. BASIS trial showed that amiodarone significantly reduced total mortality and

arrhythmic events in patients with acute MI and asymptomatic complex ventricular ectopic activity detected by continuous monitoring by 61% and 66% respectively (15). Amiodarone is included in the ACLS protocol for treatment of refractory unstable ventricular arrhythmias not responding to DC shocks in the setting of cardiac arrest. Although amiodarone was successful to increase the return of spontaneous circulation and hospital admission, it was not associated with improved overall survival(16).

Ventricular arrhythmia associated with special types of cardiomyopathy

Hypertrophic cardiomyopathy is an autosomal dominant disorder associated with ventricular arrhythmia and higher risk for SCD. Amiodarone has been used in selected patients with HCM who have evidence of ventricular arrhythmia on holter monitoring; however conflicting data exist regarding its efficacy in preventing SCD. Although amiodarone was not associated with SCD in 39 patients with repetitive NSVT (17), another study showed that 20% of patients on prophylactic amiodarone died suddenly (18). Based on the above, ICD is the treatment of choice for prevention of SCD in such patients with high risk profile however not all patients have access to such therapy due to its cost and availability.

ARVC is a condition in which there is fibro-fatty replacement of right ventricular myocardium and it is associated with ventricular arrhythmia and SCD. ICD is the most effective treatment in prevention of SCD; however amiodarone can be used in some patients to decrease the ventricular arrhythmia when ICD is not indicated or not accessible and also in patients who received multiple shocks from their ICDs either appropriate or inappropriate. When compared to other anti-arrhythmic drugs like beta blockers or sotalol, amiodarone had superior efficacy in prevention of ventricular arrhythmia in patients with ARVC (19).

Ventricular arrhythmia associated with special types of channellopathy

Brugada syndrome is a genetic of Na channel of the heart and associated with SCD and ventricular arrhythmias. ICD is the most effective treatment in prevention of SCD; however it only indicated in patients who survived cardiac arrest, spontaneous sustained VT or arrhythmic syncope. Quinidine is the most effective medication to prevent ventricular arrhythmia; however it is associated with numerous side effects due to its anticholinergic properties. Amiodarone is ineffective in preventing ventricular arrhythmia in Brugada syndrome. Also it should be avoided in such cases as it can be associated with refractory ventricular arrhythmia as it can unmask brugada pattern (20).

Long QT syndrome is a disorder of myocardial repolarization that is associated with ventricular arrhythmia and SCD. Amiodarone by its K channel blocking effect and prolongation of refractory period can be associated with further QT prolongation and risk of torsade de pointes and it should be avoided in such patients (21).

Ventricular arrhythmia in structurally normal heart

Idiopathic ventricular tachycardia occurs in the absence of structural heart disease and without evidence of channellopathy. It carries a better prognosis however it can be associated with significant symptoms or even SCD. Right ventricular outflow tract is the most common source for such VT and less commonly from LVOT or aortic cusps. Two treatment options are available either medical or catheter ablation. Ablation is the first choice as its cure rate around 90%. Amiodarone is one of the drugs that can be used if ventricular arrhythmia cannot be controlled with beta blockers or calcium channel blockers or if not tolerated or contraindicated. Also it can be considered as an alternative if ablation carries a high risk for complications like heart block. Amiodarone was successfully used in such patients with good result and no recurrence has been noted (22).

2-Supraventricular Arrhythmias:

Role of amiodarone in atrial fibrillation

Amiodarone has been used in atrial fibrillation in both acute and chronic settings. In acute setting, it is one of the most important drugs not only to restore sinus rhythm but also to maintain it and prevent the recurrence of atrial fibrillation. It should be noted that in order to revert atrial fibrillation rhythm to sinus, one should exclude the presence of left atrial appendage thrombus by TEE. However, in patients who presented with recent AF or persistent AF with more than 4 weeks adequate anticoagulation, rhythm control strategy with amiodarone is reasonable (23). In chronic setting, amiodarone is successful in restoring sinus rhythm compared to sotalol but more better in maintaining it on follow up. Improved quality of life and better exercise performance were observed more in patients who maintained in sinus rhythm as shown in SAFE-T trial (24). In AFFIRM study, Amiodarone was more effective in achieving and maintaining sinus rhythm in comparison to both sotalol and class I antiarrhythmic at one year (25). A meta-analysis included 15 trials showed that routine use of perioperative amiodarone in cardiothoracic surgery is associated with significant reduction in perioperative AF and stroke (26). AF is the most common arrhythmia in HCM and not

well tolerated due to associated diastolic dysfunction. Amiodarone is successful in cardioversion and maintenance of sinus rhythm (27).

Role of amiodarone in paroxysmal supraventricular tachycardia

Single dose of amiodarone up to 2 h infusion can be used to restore sinus rhythm and terminate paroxysmal SVT in acute setting without considerable side effect. Sinus rhythm was restored in all patients within 1 hour. Also it was noted that left atrial size correlate inversely to the dose of amiodarone required to achieve sinus rhythm (28).

Role of amiodarone in Atrial Tachycardia

Atrial tachycardia is prevalent in patients with underlying cardiac or respiratory disease. Multifocal atrial tachycardia can be treated with amiodarone infusion successfully. A refractory atrial tachycardia not responding to various antiarrhythmic medications was successfully controlled after starting amiodarone. It is suggested that amiodarone leads to decrease in automaticity and thus controlling atrial tachycardia (29).

Adverse effects of amiodarone

Despite its clinical benefits, amiodarone has multiple side effects including thyroid abnormality, lung disorder, gastrointestinal, eye and neurological diseases.

Side effects occur more frequently with prolonged use of higher doses of amiodarone.

Thyroid dysfunction:

Amiodarone can lead to hypothyroidism or hyperthyroidism

Hypothyroidism (AIH) occurs between 6-12 months of amiodarone treatment and it is more common in patient with subclinical hypothyroidism. Its prevalence estimated to be ~ 7%. AIH is more common in female with positive thyroid thyroglobulin Abs and is independent of the daily dose of amiodarone. More than 90% of patients with negative autoantibodies recover within 2-4 months after

discontinuation of amiodarone unlike whom with positive antibodies. Replacement therapy might be needed for long term in patients who fail to recover after withdrawal of amiodarone.

Two types of AIT (amiodarone induced thyrotoxicosis): Its prevalence is estimated to be from 2-12%. Type I is called iodine induced hyperthyroidism and it is related to excess production of thyroid hormone by abnormal thyroid tissue (nodular goiter, latent Graves). Type II is due to destructive thyroiditis and it occurs in patients with normal baseline thyroid function. AIT is more common in male. Amiodarone discontinuation and antithyroid drugs are recommended in patients with type I while steroid is recommended for type II and no need for amiodarone withdrawal. In some patients, thyroidectomy may be needed if other therapy failed.

Baseline thyroid function tests with anti-thyroid peroxidase antibodies is recommended and to be repeated after 3 months routinely then every 6 months or when indicated clinically (30).

Amiodarone induced pulmonary toxicity:

Diagnosis is based on clinical picture plus evidence of lung disease by radiological examination. Exclusion of heart failure, infection and malignancy is required before diagnosis. Incidence is up to 10% at 5 years follow up. Older age and higher maintenance dose are risk factors and no pulmonary toxicity occurred if average maintenance dose was less than 305 mg. Toxicity occurred between 6 days and 60 months of treatment with the highest incidence occurring during the first 12 months. Manifestations include dyspnea 70%, cough 25%, fever 21%, nausea 7%, weakness and fatigue 7%, weight loss 4% and pleuritic chest pain 4% (31). It can be fatal in some cases. Treatment is usually supportive and steroid might be needed and of course withdrawal of amiodarone.

Hepatic:

Amiodarone infusion can be associated with elevation of liver enzymes in around 5% of the patients and rarely causes acute hepatitis (32). Acute liver failure can complicate amiodarone infusion and responded well to N-acetylcysteine infusion (33).

Ocular:

The most common symptom, reported by 1.4–40.0% of patients, is colored rings around lights. The most common ocular finding is corneal epithelial opacities resembling a cat's whiskers in 70–100%

of patients and lens opacities reported in 50–60% of patients. Both are not contraindication for amiodarone therapy. Retinopathy has, rarely, been reported in association with amiodarone treatment. Optic neuropathy in patients receiving the drug for various lengths of time has been reported as having incidences of 1.3% (34).

Neurological:

The duration of therapy is the main risk factor for development of neurotoxicity. Incidence of neurotoxic reactions is 2.8% which include tremors, ataxia, peripheral neuropathy and cognitive dysfunction. (35)

Dermatological:

More commonly in the form of photosensitivity, grey discoloration is less common and affecting unprotected area of skin. The incidence ranges from 2-57%. Skin reaction occurs due to accumulation of amiodarone and its metabolite in the skin. These changes are usually reversible after drug discontinuation; however these can persist in some patients (36, 37)

Others:

Acute sterile epididymitis is reported in some cases on high doses of amiodarone infusion and this necessitates dose reduction. Usually it is reversible upon discontinuation or dose reduction (38). Rhabdomyolysis was reported in patients taking amiodarone with simvastatin (39). Amiodarone induced hypothyroidism led to acute renal failure that resolved upon withdrawal (40).

Conclusion

Amiodarone is a very strong anti-arrhythmic drug that has been used for more than 50 years in prevention and treatment of various types of ventricular and supraventricular arrhythmias. Despite being successful as anti-arrhythmic drug, most of studies did not show strong evidence for mortality benefits. Usually amiodarone is not the first line drug in treating arrhythmias and this is because it has common and sometimes life threatening side effects. Most of adverse effects occur after prolonged use and usually if the maintenance dose was relatively high; however sometimes occur acutely. Dose reduction or even drug withdrawal is essential for reversibility of these side effects but in rare cases,

adverse reaction can persist. Early identification of patients with adverse reaction needs combination of clinical, laboratory and imaging studies. Weighing the balance between benefits and risks is mandatory before prescribing amiodarone.

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